REMARKS

The present invention relates to the assay of free and complexed troponin isoforms in patient samples. Specifically, the invention describes assay methods and kits that comprise antibodies specific for various cardiac troponin forms. Assays may use an antibody or antibody cocktail that binds to one or more specific troponin form, or that binds all forms. The assay methods and kits of the present invention can be used to diagnose unstable angina and/or myocardial infarction for example.

Claims 85-96, 102-106, and 114-142 are presently pending in the instant application. Applicants have amended claims 85, 88, 91, 94, 102, 114, and 119 herein. The new and amended claims are fully supported by the instant specification, and do not introduce new matter or require a new search. These amended claims are commensurate in scope with the claims as filed, and are offered solely to assist the Examiner in understanding the claimed invention.

Notwithstanding the foregoing, Applicants expressly reserve the right to pursue subject matter no longer or not yet claimed in one or more applications that may claim priority hereto. Applicants respectfully requests reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 88 and 119 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for reciting "and/or." Applicants disagree that the phrase "and/or" renders the claim indefinite. In an effort to advance prosecution, however, Applicants have amended the claims to explicitly define the material referred to by the criticized phrase. The amendments to claims are not made for purposes of patentability, but rather to assist the Examiner in understanding the claims. Applicants respectfully submit that the foregoing amendment renders this rejection moot.

Applicant respectfully traverses the rejection of claims 86, 87, 89, 90, 92, 93, 95, 96, 103-106, 155-119, 120-123, 125-128, and 130-133 under 35 U.S.C. 112, second paragraph, as allegedly having improper antecedent basis for reciting dependent claims using an indefinite article, as in "an assay according to claim x."

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added). *See also*, MPEP § 2173.02 (An examiner "should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness.") (emphasis in original).

The skilled artisan would be reasonably apprised that the phrase the phrase "an assay according to claim x" in a dependent claim indicates that the claim refers back to and further limits claim x, in accordance with 37 C.F.R. § 1.75. For example, in their previous response, Applicants noted that MPEP 608.01(n) specifically describes the use of the indefinite article in the context of dependent claims.

In response, the Examiner argues that these examples in the MPEP refer to multiple dependent claims. There is nothing of record, however, to indicate that the skilled artisan would understand such language in the context of multiple dependent claims, but somehow would not reasonably understand the very same language in a singular dependent claim. Applicants respectfully request that the Examiner cite support for her belief that the use of an indefinite article in dependent claims is not allowed, or explain why the skilled artisan is not reasonably apprised of the scope of the invention by the claims as written.

Because the skilled artisan is reasonably apprised of the scope of the claims, Applicant respectfully submits that the claims meet the standard of 35 U.S.C. 112, second paragraph.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under

35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 114-115, 119-120, and 124-125 under 35 U.S.C. under 35 U.S.C. 102(b) as being allegedly anticipated by Bodor *et al.*, Clinical Chemistry 38: 2203 (1992). Applicants disagree that the reference provides each and every element of the claims, as required to establish a *prima facie* case of anticipation.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. Furthermore, the claims must be interpreted in light of the teaching of the specification. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). *See also,* MPEP §2131.

As discussed by Applicants in the previous response, the instant claims describe assay methods that use antibodies that specifically bind to free cardiac specific troponin isoforms and that also specifically bind to complexed cardiac specific troponin isoforms. As noted in the instant specification, cardiac specific troponin isoforms may circulate in the blood as free isoforms, and in binary and ternary complexes. Assays that fail to measure both free and complexed isoforms can significantly underestimate the concentration of cardiac specific troponin in the sample. *See, e.g.*, specification, page 18, lines 11-32.

Applicants have amended the claims herein to better define the claimed invention in view of the Examiner's comments in Paper No. 11. Specifically, the claims refer to assays that utilize antibody that binds a free cardiac specific troponin isoform, as well as binary and ternary complexes of the isoform. The amendments to claims are not made for purposes of patentability, but rather to assist the Examiner in understanding the claim.

In Paper No. 11, the Examiner contends that the Bodor *et al.* publication discloses antibodies that include "3C5.10 and 1E11.3 which are specific for only free cTnI, 5D4.1 which is

specific for cTnI only when complexed with TnC, and 5 other mAbs which are specific for both free and complexed cTnI." Paper No. 11, page 5. Whether or not this is true, however, Applicants respectfully submit that no assays equivalent to those presently claimed, in which antibody that binds a free cardiac specific troponin isoform, as well as binary and ternary complexes of the isoform, are disclosed in the Bodor *et al.* publication.

The Examiner also contends that "Bodor... further reads on the rejected claims because the claims fail to exclude those antibodies that... have skeletal troponin reactivities." Paper No. 11, page 5. This statement, however, ignores the limitations of the claims, which, as discussed above, refer to "an antibody which specifically binds [a] free cardiac specific isoform of troponin, and which specifically binds said cardiac specific isoform of troponin in a complex comprising at least one other troponin component." As noted in the specification, antibodies that specifically bind to cardiac specific isoforms of troponin are used in the assay precisely because antibodies that cross-react with skeletal isoforms can result in aberrant assay results. *See, e.g.*, specification, page 16, lines 16-31.

Therefore, because the Bodor *et al.* publication fails to teach each and every element of the instant claims, no prima facie case of anticipation has been established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

35 U.S.C. § 103

Applicant respectfully traverses the rejection of claims 85-93, 116-118, 121-123, 126-128, and 134-136 under 35 U.S.C. 103(a) as allegedly being unpatentable over Bodor *et al.*, Clinical Chemistry 38: 2203 (1992). Applicants respectfully disagree that a *prima facie* case of obviousness has been established.

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable

expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also,* MPEP §2143.

As discussed above, the Bodor *et al.* publication fails to describe any assays that use an antibody that binds a free cardiac specific troponin isoform, as well as binary and ternary complexes of the isoform. Moreover, the skilled artisan would not be motivated to provide such an assay, because, prior to the instant invention, it was not appreciated that such antibodies would be required or advantageous in order to accurately measure cardiac troponin in patient samples.

In response, the Examiner contends that "Bodor *et al.* suggest pooling antibodies and excluding those specificities and reactivities which are not desired for certain immunoassays." Whether or not this is true, neither the Bodor *et al.* publication nor any other reference of record indicates that antibodies that bind all forms of a cardiac-specific troponin isoform -- including free, binary and ternary complexes of the isoform -- should be selected from amongst the universe of possible "specificities and reactivities" for use in an assay. Indeed, prior to the instant application, it was not recognized that failure to consider the complex state of the cardiac-specific troponin isoform could lead to aberrant assay results.

Thus, in the absence of the instant specification, no motivation existed for the skilled artisan to modify the Bodor *et al.* publication in order to provide the claimed invention. *See, e.g.*, MPEP § 2143 (The teaching or suggestion to make the claimed combination must be found in the art, and not in the applicant's disclosure); MPEP § 2145(X)(B) (An obvious-to-try situation exists when the prior art gives only general guidance as to the particular form of the claimed invention or how to achieve it).

Therefore, because there is no motivation provided to modify the reference cited by the Examiner to provide the claimed invention, no *prima facie* case of obviousness has been established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 103.

Applicant also respectfully traverses the rejection of claims 94-96, 129-133, 137, and 142 under 35 U.S.C. 103(a) as allegedly being unpatentable over Katus *et al.*, Clinical Chemistry 38: 386 (1992) in view of Bodor *et al.*, Clinical Chemistry 38: 2203 (1992). Applicants respectfully disagree that a *prima facie* case of obviousness has been established.

As discussed above, the Bodor *et al.* publication fails to teach or suggest any assays that use an antibody that binds a free cardiac specific troponin isoform, as well as binary and ternary complexes of the isoform, and no reference of record indicates that such antibodies should be selected from amongst the universe of possible "specificities and reactivities." The Katus *et al.* publication does not cure this flaw in the Examiner's alleged *prima facie* case of obviousness.

The Examiner cites the Katus *et al.* publication "for his teaching of two monoclonal antibodies that are [specific for] cardiac specific isoforms of TnT," contending that "[o]ne of ordinary skill in the art... would have reasonable expectation of success in developing and characterizing monoclonal antibodies that specifically bind free and complexed forms such as those developed and characterized by Bodor." Paper No. 11, pages 6-7. As discussed above, however, even if antibodies equivalent to those disclosed in the Bodor *et al.* publication were produced, nothing of record suggests selecting an antibody that binds all forms of a troponin isoform -- including free, binary and ternary complexes of the isoform -- for use in an assay. The skilled artisan would not be motivated to provide assays that use such antibodies because, prior to the instant invention, it was not appreciated that such antibodies would be required or advantageous in order to accurately measure cardiac troponin in patient samples.

Therefore, because there is no motivation provided to modify the reference cited by the Examiner to provide the claimed invention, no *prima facie* case of obviousness has been established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 103.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,
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Appendix A: Marked up amended claims showing changes made

85. (Twice amended) An assay for determining the presence or amount of a free and complexed cardiac specific isoform of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds said free cardiac specific isoform of troponin, and which specifically binds said cardiac specific isoform of troponin in a binary complex comprising [at least] one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds said cardiac specific isoform of troponin in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoform of troponin, wherein said signal is at least a factor of two larger than a signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific isoform of troponin; (ii) troponin complexes which do not comprise said cardiac specific isoform of troponin; or (iii) a combination of (i) and (ii), and wherein said signal is related to the presence or amount of said free and complexed cardiac specific isoform of troponin in said sample.

88. (Twice amended) An assay for determining the presence or amount of a free and complexed cardiac specific isoform of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin I and[/or] cardiac specific troponin T, and which specifically binds to cardiac specific troponin I and[/or] cardiac specific troponin T in a complex comprising at least one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds to cardiac specific troponin I and cardiac specific troponin T in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoform of troponin, wherein said signal is at least a factor of two larger than a minimum signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific isoform of troponin; (ii) troponin complexes which do not comprise said cardiac specific isoform of troponin; or (iii) a combination of (i) and (ii), and wherein said signal is related to the presence or amount of said free and complexed cardiac specific isoform of troponin in said sample.

91. (Twice amended) An assay for determining the presence or amount of free and complexed cardiac specific troponin I in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin I, and which specifically binds to cardiac specific troponin I in a complex comprising at least one other troponin component selected from the group consisting of troponin C and troponin T, and which specifically binds to cardiac specific troponin I in a ternary complex comprising troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific troponin I, wherein said signal is at least a factor of two larger than a signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific troponin I; (ii) troponin complexes which do not comprise said cardiac specific troponin I; or (iii) a combination of (i) and (ii), and wherein said detectable signal is related to the presence or amount of said free and complexed cardiac specific troponin I in said sample.

94. (Twice amended) An assay for determining the presence or amount of free and complexed cardiac specific troponin T in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin T, and which specifically binds to cardiac specific troponin T in a complex

comprising at least one other troponin component selected from the group consisting of troponin C and troponin I, and which specifically binds to cardiac specific troponin T in a ternary complex comprising troponin C and troponin I; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific troponin T, wherein said signal is at least a factor of two larger than a signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific troponin T; (ii) troponin complexes which do not comprise said cardiac specific troponin T; or (iii) a combination of (i) and (ii), and wherein said detectable signal is related to the presence or amount of said free and complexed cardiac specific troponin T in said sample.

102. (Twice amended) An assay for determining the presence or amount of all free and complexed cardiac specific isoform of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds [any] all free cardiac specific isoforms of troponin, and which specifically binds [any] all cardiac specific isoforms of troponin in a complex comprising at least one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds all cardiac specific isoforms of troponin in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoforms of troponin, wherein said signal is related to the presence or amount of all free and complexed cardiac specific isoform of troponin in said sample.

114. An assay for determining the presence or amount of a free and complexed cardiac specific isoform of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds said free cardiac specific isoform of troponin, and which specifically binds said cardiac specific isoform of troponin in a complex comprising at least one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds said cardiac specific isoform of troponin in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoform of troponin, wherein said signal is related to the presence or amount of said free and complexed cardiac specific isoform of troponin in said sample.

119. (Amended) An assay for determining the presence or amount of a free and complexed cardiac specific isoform of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin I and[/or] cardiac specific troponin T, and which specifically binds to cardiac specific troponin I and[/or] cardiac specific troponin T in a complex comprising at least one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds to cardiac specific troponin I and cardiac specific troponin T in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoform of troponin, wherein said signal is related to the presence or amount of said free and complexed cardiac specific isoform of troponin in said sample.